Acute Respiratory Distress Syndrome in the Global Context

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ABSTRACT

Acute respiratory distress syndrome (ARDS) is a clinically defined syndrome of hypoxia and bilateral pulmonary infiltrates due to inflammatory pathways triggered by pulmonary and nonpulmonary insults, and ARDS is pathologically correlated with diffuse alveolar damage. Estimates of ARDS's impact in the developed world vary widely, with some of the discrepancies attributed to marked differences in the availability of intensive care beds and mechanical ventilation. Almost nothing is known about the epidemiology of ARDS in the developing world, in part due to a clinical definition requiring positive pressure ventilation, arterial blood gases, and chest radiography. Current frameworks for comparing the epidemiology of death and disability across the world including the GBD (Global Burden of Disease Study) 2010 are ill-suited to quantifying critical illness syndromes including ARDS. Modifications to the definition of ARDS to allow a provision for environments without the capacity for positive pressure ventilation, and to allow for alternate diagnostic techniques including pulse oximetry and ultrasound, may make it possible to quantify and describe the impact of ARDS in the global context.

In 1967, Ashbaugh et al. [1] described 12 patients receiving respiratory support who were noted to have bilateral infiltrates on chest radiograph; decreased lung compliance; hyperemia, engorged vessels, and hyaline membranes on pathology; and who "did not respond to usual methods of therapy." From this remarkable set of observations, the acute respiratory distress syndrome (ARDS) was born. Its definition was first operationalized by the 1994 American European Consensus Conference (AECC) [2]. ARDS was defined as a syndrome of acute onset, oxygenation impairment of partial arterial oxygen tension/fractional concentration of oxygen in inspired gas (PaO_2/FiO_2) <200 mm Hg regardless of positive end-expiratory pressure (PEEP) level, bilateral infiltrates on frontal chest radiograph, and pulmonary artery wedge pressure ≤18 mm Hg or no clinical evidence of left atrial hypertension. Acute lung injury carried the same definition except that oxygenation was less impaired: PaO_2/FiO_2 <300 mm Hg. Mechanical ventilation was excluded as a requirement with the explicit recognition that its use varies by resource availability and practice patterns. In addition, whereas PEEP was known to have a profound effect on oxygenation, it was thought to have too inconsistent an effect to include in the definition. Also explicitly noted were the fact that even mild infiltrates would meet criteria, and that infectious causes of the syndrome (bilateral pneumonia) would not be excluded.

The next redefining of the syndrome occurred in 2012, with the Berlin definition [3]. This consensus statement sought to correct deficiencies in feasibility, reliability, and validity of the 1994 definition. The Berlin definition of ARDS requires:

- onset within 1 week of a known clinical insult;
- bilateral opacities on chest radiograph or computed tomography scan not fully explained by effusions, lobar/lung collapse, or nodules;
- respiratory failure not fully explained by cardiac failure or fluid overload (objective assessment needed with echocardiography only if no clear risk factor present); and
- oxygenation of PaO_2/FiO_2 ≤300 mm Hg with PEEP of at least 5 cm H_2O.

With the Berlin definition, acute lung injury is no longer a category, and severity of ARDS is divided by PaO_2/FiO_2 ratio (≤300 cm H_2O mild, ≤200 cm H_2O moderate, ≤100 cm H_2O severe.)

The inclusion of a minimum PEEP of 5 cm H_2O as a requirement in the Berlin definition was on the basis of evidence that PEEP can have a large effect on the PaO_2/FiO_2 ratio [4]. The Berlin panel made this addition on the basis of its "face validity," without specific testing of the effect of various PEEP levels. The earlier AECC panel also explicitly noted the effect of PEEP on the PaO_2/FiO_2 ratio, but did not include a particular PEEP level as a requirement given PEEP's inconsistent effect on the PaO_2/FiO_2 ratio, as well as differences in the availability of mechanical ventilation in different areas of the world.

The current ARDS definition is an improvement over the 1994 definition, enabling better comparisons for trials designed to test interventions. However, it is difficult to apply in resource-poor settings. As noted in the editorial accompanying the publication of the Berlin definition, "the latest definition, by specifying PEEP requirements when measuring the PaO_2/FiO_2 ratio, has essentially excluded ARDS as a possible diagnosis in patients without ventilation. Around the world, many individuals develop critical illness far from the modern intensive care unit (ICU). Hopefully, this new Berlin definition for ARDS will not inadvertently compromise efforts to develop and disseminate strategies for the care of such patients through unintended mislabeling" [5].

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PATHOPHYSIOLOGY

ARDS is thought to begin with lung injury precipitated by any of a large number of "clinical insults" [3]. The usual categories are shock, sepsis, pneumonia, aspiration, pancreatitis, blood transfusion, drug overdose, high-risk surgery, high-risk trauma, and "other" [6,7]. These are often divided into "direct" or pulmonary causes versus "indirect" or nonpulmonary causes, though no consistent difference in mortality has been demonstrated on the basis of a direct versus indirect cause [8–10]. Beyond these predisposing conditions, additional patient characteristics, or "risk modifiers," have been identified that increase the probability that a given patient will develop ARDS: history of alcohol abuse; obesity; hypoalbuminemia; chemotherapy; initial FiO_2 >0.35; respiratory rate >30 breaths per minute; functional oxygen saturation (SpO_2) <95%, arterial pH <7.35; and presence of diabetes mellitus [6].

Alveolar injury in ARDS results in the release of proinflammatory cytokines leading to damage to the vascular endothelium and alveolar epithelium [11]. ARDS progresses through 3 definite phases, though not all patients experience all phases. The first phase is the acute or exudative phase, which is characterized by inflammation, pulmonary edema, and capillary leak, resulting in refractory hypoxemia and decreased lung compliance. The abnormalities are heterogeneous, with greater consolidation usually found in dependent portions of the lungs. In some patients, the acute phase is followed by the second phase of fibrosing alveolitis characterized by continued hypoxemia, worsening pulmonary compliance, and pulmonary hypertension. Pulmonary hypertension is likely caused by a combination of factors including airway collapse, microthrombi in pulmonary vessels, vascular compression from positive pressure mechanical ventilation, and vasoconstriction due to hypoxemia, hypercarbia, and the release of vasoconstrictive substances [12]. The recovery phase involves gradual improvement in hypoxemia, with full resolution of radiologic abnormalities and return of normal pulmonary function for many survivors [11].

The pathologic correlate in the acute phase of ARDS is diffuse alveolar damage (DAD) consisting of hyaline membranes with edema, cell necrosis, and/or fibrosis; however, in an autopsy study of 356 patients who met the clinical definition for ARDS at the time of death, only 45% of patients met criteria for DAD on autopsy [13]. The clinically defined syndrome is heterogeneous, comprising patients with DAD, pneumonia, pulmonary hemorrhage, pulmonary edema, cancer, tuberculosis, abscess, fibrosis, pulmonary embolism, emphysema, and even some without a pulmonary lesion [13]. However, the specificity of the clinical definition to its pathologic correlate of DAD increases considerably when confined to "severe" ARDS as defined by the Berlin definition. In addition, it is reassuring that even with this heterogeneity of pathologic findings, clinical trials have identified interventions that decrease mortality for ARDS patients as defined by clinical, not pathologic, criteria [14,15].

EPIDEMIOLOGY

The global impact of ARDS is difficult to estimate. The GBD (Global Burden of Diseases, Injuries, and Risk Factors Study) 2010 sought to estimate causes of death for the populations of 187 countries categorized into 21 regions of the world with 235 causes [16]. It separated causes of death into 3 broad categories: 1) communicable, maternal, neonatal, and nutritional disorders; 2) noncommunicable diseases; and 3) injuries. Although this study represents an impressive analysis of global disease incidences and trends, it offers little insight into the epidemiology of ARDS, which can result from and accompany disorders in all 3 categories [17].

Adhikari et al. [18] note that defining the burden of critical illness including ARDS is also difficult due to changing definitions, requirement of multiple clinical data points, brief periods of illness that decrease prevalent cases at a given point in time relative to chronic diseases, and the fact that most studies are confined to ICUs, with ICU capacity varying widely between countries. They estimate the burden of ARDS by World Bank region using population estimates and applying ARDS incidences from developed countries, but they note that the estimates necessarily rely on the assumption that population structure, underlying risk factors, and critical care capacity are similar between the developed world and developing world.

ARDS epidemiology in the developed world

The estimates we have for ARDS incidence all originate in the developed world. In Table 1, we present the most recent population-based estimates representing various parts of the developed world. Estimates of ARDS (previously acute lung injury, PaO_2/FiO_2 <300 mm Hg) even in these studies vary from 10.1 to 86.2 cases per 100,000 person-years.

All of these studies are based on the screening of ICU patients, and all use a version of the 1994 AECC criteria. All but the Scandinavian study [19] require mechanical ventilation for inclusion, though mechanical ventilation was not required by the AECC definition. Explanations for the large variability in incidence estimates are many: true differences in underlying risk factors for ARDS including critical care interventions; the potential for seasonal variation not captured in studies of brief duration; misclassification due to varying chest radiograph interpretations; differences in methodology; true incidence changes over time; and differences in ICU bed availability and use (Table 2) [7,20].

ICU bed availability varies widely across global jurisdictions. Because only patients in ICUs were screened for ARDS in these studies, variability in ICU bed concentration will affect ARDS incidence estimates. In this way, we esti-

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